Translation

PCT/JP2003/016601

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference W1360-00	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/JP2003/016601	International filing date (*day/month/year*) 24 December 2003 (24.12.2003)	Priority date (*day/month/year*) 26 December 2002 (26.12.2002)
International Patent Classification (IPC) or national classification and IPC G01N 33/543		
Applicant NITTO BOSEKI CO., LTD.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report
   ☐ Box No. II Priority
   ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   ☒ Box No. IV Lack of unity of invention
   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   ☐ Box No. VI Certain documents cited
   ☐ Box No. VII Certain defects in the international application
   ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 May 2004 (12.05.2004)	30 August 2004 (30.08.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2003/016601

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is language of a translation furnished for the purpose of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ The international application as originally filed/furnished

☒ the description:

pages 1-23, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

pages 2-12, as originally filed/furnished

pages* _____, as amended (together with any statement) under Article 19

pages* 1 received by this Authority on 13 August 2004 (13.08.2004)

pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-3, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP03/16601

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

Whereas the inventions of claims 1-11 concern an immunological measurement using a first antibody and a second antibody, the invention of claim 12 is a marker per se for the diagnosis of bone disease comprising a tartrate resistant acid phosphatase fragment with no relationship whatsoever to the former.

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____ .

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP03/16601

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims	3-6, 12	YES
	Claims	1, 2, 7-11	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: JP 60-501674 A (Ekins, Roger Philip) October 3, 1985, Claims & WO 85/00226A & EP 149631 A & GB 8317124 A & DE 3475351 A & US 4745072 A

Claims 1, 2, and 7-11

Document 1 cited in the international search report describes a method that uses two types of antibodies to measure a target substance in a sample wherein a free ligand (target substance) and a ligand analogue (competitive substance) are present concurrently, and more specifically, it is a method for competitive immunological measurement that uses a free ligand (target substance), a ligand analogue (competitive substance), a specific binding agent (first antibody) and an exogenous binding agent (second antibody) (see claims).

Differences with document 1 that are not based on the descriptions of the claims of this application such as a discussion concerning endogenous substances, the binding order of the second antibody, etc., cannot be taken into consideration when evaluating the patentability of this application, and therefore the inventions of claims and 1, 2, and 7-11 lack an inventive step.

Claims 3-6

Although document 1 describes a method for competitive immunological measurement that uses a free ligand (target substance), a ligand analogue (competitive substance), a specific binding agent (first antibody) and an exogenous binding agent (second antibody), the substances that come to mind as ligands are homeostatic hormones, etc. Document 1 neither describes nor suggests using an active enzyme such as a tartrate resistant acid phosphatase as a target substance and making the enzymatic degradation product a competitive substance. As a result, the inventions of claims 3-6 are novel and involve an inventive step.

Claim 12

None of the documents cited in the international search report describes nor suggests that the fragment such as the one of claim 12 can be used as a marker for the diagnosis of bone disease.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 2, and 7-11 do not make the active form of an enzyme the focus of a discussion, but because the Specification of this application discusses tartrate resistant acid phosphatase, which is essentially an active form of an enzyme, from a technical standpoint the Specification of this application does not sufficiently support items other than those wherein the active form of an enzyme is the focus.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP03/16601

Box No. I Basis of the report

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☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-23 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

Nos. 2-12 as originally filed/furnished

Nos.* _____ as amended (together with any statement) under Article 19

Nos.* 1 received by this Authority on August 13, 2004

Nos.* _____ received by this Authority on _____

☒ the drawings:

sheets/~~figs~~ 1-3 as originally filed/furnished

sheets/figs* _____ received by this Authority on _____

sheets/figs* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded".*

Translation of PCT Article 34

Amendment

CLAIMS

1.(Amended) An immunoassay method in which a target substance in a specimen containing the target substance together with a competitive substance therein is assayed by the use of two types of antibodies, and which comprises

using the two types of the antibodies, i.e., a first antibody and a second antibody which have the following properties: (i) the first antibody has affinity for the target substance and the competitive substance, (ii) the first antibody has a higher affinity for the target substance than for the competitive substance, (iii) the second antibody has a higher affinity for the competitive substance than for the target substance, and (iv) the affinity for the competitive substance of the second antibody is higher than the affinity for the target substance of the first antibody,

bonding the target substance and the competitive substance in the specimen to the first antibody and second antibody adsorbed on a carrier, and then

measuring the level of the bonded target substance to assay the target substance in said specimen.

2. An immunoassay method according to claim 1, wherein furthermore, the affinity for the target substance of the second antibody is higher than the

affinity for the competitive substance of the first antibody.

3. An immunoassay method according to claim 1 or 2, wherein the target substance is an intact enzyme and the measurement of the level of the target substance bonded is the measurement of the enzymatic activity of said intact enzyme.

4. An immunoassay method according to claim 3, wherein the competitive substance is a substance not having said enzymatic activity.

5. An immunoassay method according to claim 3 or 4, wherein the competitive substance is an enzyme degradation product.

6. An immunoassay method according to any one of claims 3 to 5, wherein the intact enzyme is tartrate resistant acid phosphatase 5b (TRACP 5b).

7. An immunoassay method according to any one of claims 1 to 6, wherein the carrier is an insoluble solid support.

8. An immunoassay method according to any one of claims 1 to 7, wherein the carrier on which the first antibody is adsorbed is a solid support, and the second antibody is adsorbed on a carrier dispersed in a solution or is dissolved.

9. A kit for immunoassay of a target substance in a specimen by the use of two types of antibodies, which comprises

the two types of the antibodies, i.e., a

first antibody and a second antibody which have the following properties: (i) the first antibody has affinity for the target substance and a competitive substance, (ii) the first antibody has a higher affinity for the target substance than for the competitive substance, (iii) the second antibody has a higher affinity for the competitive substance than for the target substance, and (iv) the affinity for the competitive substance of the second antibody is higher than the affinity for the target substance of the first antibody.

10. A kit according to claim 9, wherein the first antibody and the second antibody are adsorbed on a carrier.

11. A kit according to claim 9 or 10, wherein the first antibody is adsorbed on a solid support and the second antibody is adsorbed on a carrier dispersed in a solution or is dissolved.

12. A marker molecule for diagnosing bone disease, comprising a fragment of tartrate resistant acid phosphatase 5b (TRACP 5b) having a molecular weight of approximately 5580 Da, 5795 Da, 6860 Da or 7075 Da.